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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/802,829	08/03/2004	Dale J. Kempf	7050.US.02	4276

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EXAMINER	
HENLEY III, RAYMOND J	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 04/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/802,829	KEMPF ET AL	
	Examiner	Art Unit	
	Raymond J. Henley III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 August 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *November 26, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

CLAIMS 1-18 ARE PRESENTED FOR EXAMINATION

Applicants' Information Disclosure Statement filed November 26, 2004 has been received and entered into the application. As reflected by the attached, completed copy of form PTO-1449, the Examiner has considered the references cited by Applicants.

Claim Rejection - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 8 and 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a disease, disorder or adverse effect caused by an elevated serum concentration of an UGT1A1 substrate upon administration of an active pharmaceutical ingredient selected from the group consisting of indinavir, atazanavir, amphotericin B/cholesteryl sulfate complex, testosterone, interferon beta-1b, bicalutamide, ciprofloxacin, oxaliplatin, floxuridine, gemcitabine hydrochloride, sargramostim, gemtuzumab ozogamicin, vinorelbine tartrate, carboplatin, peginterferon alpha-2B, tacrolimus, aldesleukin, dalfopristin/quinupristin, didanosine and capecitabine, does not reasonably provide enablement for the above method where the pharmaceutical ingredient is unspecified, as in present claim 7. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims without a burden of undue experimentation.

While it is noted that the present disclosure describes a method for treating a disease, disorder or adverse effect caused by an elevated serum concentration of an UGT1A1 substrate upon administration of an active pharmaceutical ingredient, (e.g., see the present specification at page 4, lines 6-9, the disclosure does not furnish guidance or direction in selecting the particular pharmaceutical ingredient, other than those listed, i.e., indinavir, atazanavir, amphotericin B/cholesteryl sulfate complex, testosterone, interferon beta-1b, bicalutamide, ciprofloxacin, oxaliplatin, floxuridine, gemcitabine hydrochloride, sargramostim, gemtuzumab ozogamicin, vinorelbine tartrate, carboplatin, peginterferon alpha-2B, tacrolimus, aldesleukin, dalfopristin/quinupristin, didanosine and capecitabine, (e.g., see the present specification at page 4, lines 9-13), to administer, or provide adequate information that would narrow the astronomical range of possible candidate compounds represented by the bare expression in claim 7 "an active pharmaceutical ingredient". Thus, one skilled in the art would have to engage in undue experimentation in order to determine which compounds, from the vast number of compounds known, would, upon administration, cause an elevated serum concentration of an UGT1A1 substrate, (e.g., bilirubin or estriol, see the present specification at page 1, line 18).

The present disclosure does no more than describe the desired function of the "pharmaceutical ingredient" that would be useful in the method of claim 7. At best, the present specification simply indicates that one should run tests on an finite, but astronomical, number of possible compounds in the hope that at least one of them will be suitable in the practice of the claimed method. In particular, the disclosure indicates that "Unconjugated hyperbilirubinemia is an undesirable disease or disorder or adverse effect which is caused by administration to a subject of medicaments such as, for example, indinavir, atazanavir, amphotericin B/cholesteryl

sulfate complex, testosterone, interferon beta-1b, bicalutamide, ciprofloxacin, oxaliplatin, floxuridine, gemcitabine hydrochloride, sargramostim, gemtuzumab ozogamicin, vinorelbine tartrate, carboplatin, peginterferon alpha-2B, tacrolimus, aldesleukin, dalfopristin/quinupristin, didanosine and capecitabine.", (present specification at page 4, lines 7-13). This is the full extent of Applicants' disclosure of which medicaments may cause unconjugated hyperbilirubinemia. Nowhere, however, does the disclosure specify which other medicaments would cause unconjugated hyperbilirubinemia or a teaching of how one would go about identifying a population of such medicaments, other than those specifically disclosed. That which is disclosed by Applicants appears to be no more than an invitation to experiment and discover other such medicaments which cause unconjugated hyperbilirubinemia. However, such does not meet the requirements of 35 U.S.C. § 112, first paragraph that the "specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same".

Lacking such a disclosure of other medicaments which cause unconjugated hyperbilirubinemia or a means by which such compounds could be identified, it is not seen that another party, i.e., the skilled artisan, could be lead in any manner so as to do that which the inventors themselves have not done, i.e., identify such compounds, other than those disclosed, which cause unconjugated hyperbilirubinemia. The present disclosure is not seen to do any more than outline the goals which the inventors hope to achieve and the problems that the invention will hopefully ameliorate. This, however, does not satisfy the disclosure requirement under 35 U.S.C. § 112, first paragraph, as noted above.

The Examiner is aware that "The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971).", (see MPEP § 2164.03). "However, in applications directed to inventions in arts where the results are unpredictable, [such as here where the art is medicine] the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as ***most*** chemical reactions ***and physiological activity***, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).", (emphasis added; *Id.*).

Accordingly, the claims are properly rejected.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

I Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "consisting essentially of", as employed in a Markush grouping, is of indeterminate scope which therefore does not clearly set forth the metes and bounds of the grouping of elements intended to be covered.

In this regard, the Examiner is guided in his opinion by MPEP § 2111.03 which indicates that a Markush group is intended to be a closed grouping of elements, "In contrast, the court noted the phrase "group consisting of" is a closed term, which is often used in claim drafting to signal a "Markush group" *that is by its nature closed*.", (emphasis added). Also, because "It is improper to use the term 'comprising' instead of 'consisting of.' *Ex parte Dotter*, 12 USPQ 382 (Bd. App. 1931).", and because "consisting essentially of" here is interpreted as comprising because the present specification fails to set forth the basic and novel characteristics of grouped elements, i.e., see MPEP § 2111.03, "For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, 'consisting essentially of' will be construed as equivalent to 'comprising.' See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 ("PPG could have defined the scope of the phrase consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention.").", present claim 9 constructively reads as "selected from the group comprising indinavir...", which, for the reasons above, is not proper and renders the claimed subject matter indefinite.

In order to overcome this point of rejection, it is suggested that "consisting essentially of" be changed to ---consisting of---.

II Claims 13-18 are also rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are considered indefinite because claims 13 and 16 are incomplete for omitting an essential element of the claimed method, which element is a host to whom the effective amount of ritonavir is administered.

In order to overcome this point of rejection, it is suggested that claims 13 and 16 be amended to include a host, e.g., claim 13 should be amended as "13. A method for increasing glucuronidation of an UGT1A1 substrate comprising the step of administering an effective amount of ritonavir to a subject .".

Accordingly, the claim is properly rejected.

Legal Standard for Anticipation/Inherency Under - 35 USC § 102

To anticipate a claim under 35 U.S.C. § 102, a single prior art reference must place the invention in the public's possession by disclosing each and every element of the claimed invention in a manner sufficient to enable one skilled in the art to practice the invention. *Scripps Clinic & Research Foundation v. Genetech, Inc.,* 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1001 (Fed. Cir. 1991); *In re Donahue,* 766 F2d531, 533, 226 U.S.P.Q. 619, 621 (Fed. Cir. 1985). To anticipate, the prior art must either expressly or inherently disclose every limitation of the claimed invention. *MEHL/Biophile Int'l Corp. v. Milgraum,* 192 F.3d 1362, 1365, 52 U.S.P.Q.2d 1303, 1303 (Fed. Cir. 1999) (citing to *In re Schreiber,* 128 F.3d 1473, 1477, 44 U.S.P.Q. 1429, 1431 (Fed. Cir. 1997)); *Atlas Powder Co. v. Ireco Inc.,* 190 F.3d 1342, 1347, 51 U.S.P.Q.2d 1943, 1946 (Fed. Cir. 1999). To inherently anticipate, the prior art must necessarily function in accordance with, or include, the claimed limitations. *MEHL/Biophile,* 192 F.3d at 1365, 52 U.S.P.Q.2d at 1303. However, it is not required that those of ordinary skill in the art recognize the inherent characteristics or the function of the prior art. *Id.* Specifically, discovery

of the mechanism underlying a known process does not make it patentable. See also MPEP §§ 2112, 2112.02 and 2145(II).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I Claims 1-9 and 11-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Agarwala et al., (cited by Applicants as reference "C1"; with an apparent date of September 2002). It is requested that, if possible, Applicants submit another copy of this reference. The current copy is of poor quality.

Agarwala et al. teach a method of administering ritonavir, ("RTV"), with atazanavir, ("ATV"), for the purpose of evaluating the dosing regimen of ATV 300 mg/RTV 100 mg qd, (a.k.a., every day), (see present claims 6, 8, 15 and 18 which provide for such a dose of RTV in setting forth "the effective amount of ritonavir is in the range of about 25 to about 1200 mg daily") for potential use in further Phase III studies, (see col. 2, under the heading "Background"). The above teachings also meet the claim requirements for the additional administration of ATV as provided for in claims 1, 13 and 16, (i.e., "comprising" allows for the administration of active agents other than those specifically set forth), 7, "upon administration of an active pharmaceutical ingredient", 9, "wherein the pharmaceutical ingredient is selected from the group consisting essentially of ... atazanavir...", and 11, "the active pharmaceutical ingredient

is atazanavir". Such comments also apply to the claims dependent on the claims specifically mentioned above.

Agarwala et al. also disclose that "reversible elevated bilirubin" was one of the most frequently reported adverse event in patients receiving the combination of ATV 300 mg and RTV 100 mg as well as jaundice (col. 5, under the heading "safety"). While "unconjugated" bilirubin is not set forth, the Examiner has reason to believe that such was inherently the case because conjugated bilirubin would have been excreted in the feces as acknowledged by Applicants at page 1, lines 23-26).

The elevated bilirubin, (a.k.a., hyperbilirubinemia) was apparently due to, at least, the ATV administration, given that reversible elevated bilirubin was seen in the patients receiving ATV alone (see col. 5, under the heading "safety"). Such is seen to meet the claim requirements of 1 and 7 for at least "adverse effect" or "disorder" and for those claims requiring an "UGT1A1 substrate", which is bilirubin, (e.g., see claims 3, 14 and 17).

While Agarwala et al. are silent with respect to the effect of RTV on the induction of UGT1A1 isoform expression, (claim 1), increasing glucuronidation of an UGT1A1 substrate, (claim 13), or increasing the excretion of an UGT1A1 substrate, (claim 16), such claim elements are deemed inherent in the method of Agarwala et al. because in both the present claims and the method of Argarwala et al., the same drug is administered in the same manner, in the same dosage and in the same host. Further, with respect to the requirement in claim 7 that the elevated UGT1A1 substrate adverse effect, i.e., the hyperbilirubinemia itself, is treated appears to be the case because in the patients treated only with ATV, there was a 57% incidence of hyperbilirubinemia, while in those treated with both ATV and RTV, the incidence was less, i.e.,

apparently 50%. Also, see MPEP § 2112, which sets forth the requirements for rejecting claims on the basis of the concept of inherency. The Examiner believes that the requirements set forth therein have been met in the above statement of rejection.

Accordingly, the claims are properly rejected.

II Claims 13-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Norbeck et al. (U.S. Patent No. 6,037,157 ; cited by Applicants as reference "A1").

Norbeck et al. teach the daily administration of 600mg of ritonavir, (see col. 10, lines 54-63, especially lines 58-59 "ritonavir 200 mg of liquid formulation every 8 hours", i.e., 3 x 200mg = 600mg), to human volunteers. As acknowledged by Applicants', the UGT1A1 substrate, bilirubin, is endogenous, (specification at page 1, lines 17-19). This is also taught by Ritter et al., (cited by Applicants, reference "C4"; see the paragraph bridging cols. 1-2 on page 476, "Bilirubin is an endogenous waste product generated from the metabolism of heme...").

Because in both the present claims and in Norbeck et al., the same compound, i.e., ritonavir, would be present in the same physiological environment, i.e., in the presence of bilirubin, which is also referred to as "an UGT1A1 substrate" in present claims 13 and 16, it must then necessarily follow that the claimed "increasing glucuronidation", (claim 13), and "increasing excretion of an UGT1A1 substrate", would be inherent in the method of Norbeck et al.

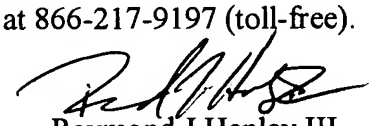
Accordingly, the claims are properly rejected.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond J. Henley III whose telephone number is 571-272-0575. The examiner can normally be reached on M-F, 8:30 am to 4:00 pm Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Raymond J Henley III
Primary Examiner
Art Unit 1614

April 13, 2006